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invited review

Vasoconstrictor and vasodilator effects of adenosine in the kidney

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Hansen, Pernille B., and Jurgen Schnermann. Vasoconstrictor and vasodilator effects of adenosine in the kidney. *Am J Physiol Renal Physiol* 285: F590–F599, 2003; 10.1152/ajprenal.00051.2003.—Adenosine is an ATP breakdown product that in most vessels causes vasodilatation and that contributes to the metabolic control of organ perfusion, i.e., to the match between oxygen demand and oxygen delivery. In the renal vasculature, in contrast, adenosine can produce vasoconstriction, a response that has been suggested to be an organ-specific version of metabolic control designed to restrict organ perfusion when transport work increases. However, the vasoconstriction elicited by an intravenous infusion of adenosine is only short lasting, being replaced within 1–2 min by vasodilatation. It appears that the steady-state response to the increase of plasma adenosine levels above normal resulting from the infusion is global renal vasorelaxation that is the result of A_2AR activation in most parts of the renal vasculature, including larger renal arteries, juxtamedullary afferent arterioles, efferent arterioles, and medullary vessels. A_2AR-mediated vasorelaxation is probably facilitated by endothelial receptors that cause the release of nitric oxide and other endothelial relaxing factors. In contrast, isolated perfused afferent arterioles of superficial and midcortical nephrons of rabbit and mouse, especially in their most distal segment at the entrance to the glomerulus, respond to adenosine with persistent vasoconstriction, indicating predominant or exclusive expression of A_1AR. A_1AR in afferent arterioles are selectively activated from the interstitial aspect of the vessel. This property can dissociate A_1AR activation from changes in vascular adenosine concentration, a characteristic that is ideally suited for the role of renal adenosine as a paracrine factor in the control of glomerular function.

adenosine receptors; vascular resistance; renal blood flow; endothelium

THE EXTRACELLULAR ACTIONS of adenosine are mediated by binding of the nucleoside to four types of G protein-coupled membrane receptors, A_1, A_{2a}, A_{2b}, and A_3 adenosine receptors (A_1AR, A_{2a}AR, A_{2b}AR, A_3AR). The expression pattern of adenosine receptor subtypes throughout the organism is extremely widespread, commensurate with the organismwide actions of the nucleoside. In most blood vessels, adenosine elicits marked vasodilatation, and this effect is mediated by A_{2a}AR and A_{2b}AR, G protein-coupled receptors that induce relaxation through the $G_s\alpha$ and protein kinase A pathway. Adenosine-induced vasodilatation reflects dominance of A_2AR in the vasculature of most tissues and organs. In contrast, A_1AR coupled to $G_i\alpha$ and PLC activate motor activity of smooth muscle cells in a number of muscular tissues (4, 44, 65, 67), but this receptor subtype is not widely expressed in the vasculature. A_1AR are, however, present in blood vessels of the kidney besides A_2AR, and this has made the renal vascular actions of adenosine comparatively complex.

Evidence obtained in the 1960s solidified an earlier observation that the kidney vasculature differs from other vascular beds in that the overall effect of exogenous adenosine may be vasoconstriction (17, 24, 81). This remarkable observation of a constrictor effect exerted by a prototypical metabolic dilator has been the focus of numerous discussions, but its understanding is still incomplete. A renewed interest in the vasoconstrictor action of adenosine has resulted from the recent evidence in support of the notion that the nu-

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cleoside is responsible for the afferent arteriolar constriction caused by increasing NaCl concentration at the macula densa, the so-called tubuloglomerular feedback (TGF) response (10, 76, 80). Although the vasoconstrictor potential of adenosine at the organ level has been the origin of the proposal of adenosine acting as the constrictor mediator of the TGF response (55), this reasoning has always been weakened by an apparent, but not fully acknowledged, internal inconsistency. The main problem has been that the vasoconstriction and the accompanying decrease in renal blood flow at the organ level are only a transient phenomenon, whereas the steady-state effect of adenosine is either no change or an increase in renal blood flow (23, 52, 54, 74, 77). Thus the temporal characteristics of the effects of changes in adenosine levels on global renal vasoconstriction and on TGF-induced vasoconstriction are apparently entirely different, making it difficult to accept that these responses are mediated by the same receptors (51). Because the kidney vasculature is sufficiently heterogeneous, it has been common to argue that adenosine causes vasoconstriction in one part of the renal vascular bed and vasodilatation in another, for example, that afferent arteriolar vasoconstriction is accompanied and overcome by efferent vasodilatation (77) or that superficial vasoconstriction is accompanied and overcome by juxtamedullary vasodilatation (58).

In the present review, we make an attempt to reconcile the failure of adenosine to cause a lasting global renal vasoconstriction with its ability to markedly and persistently elicit vasoconstriction at the arteriolar level, both pharmacologically and in its presumed physiological equivalent, the TGF response. Our overall conclusion is that the dominant effect of exogenous adenosine in the whole kidney is vasodilatation, which like in other vascular beds is a reflection of the wide distribution of A_2AR in the renal vasculature and their activation by the supranormal adenosine levels resulting from the infusion. However, the distal afferent arteriole at the entrance to the glomerulus constricts to adenosine over a much wider concentration range than any other vascular segment, perhaps reflecting predominant or exclusive expression of A_1AR. Because the region of A_1AR-mediated vasoconstriction at high adenosine concentrations is restricted to a narrow segment, the effect of A_1AR activation on total renal vascular resistance can be overcome when adenosine levels exceed normal concentrations and A_{2b}AR in other parts of the renal vasculature are fully engaged.

EXPRESSION OF ADENOSINE RECEPTORS IN THE KIDNEY

The scarcity of reliable antibodies and radiolabeling probes and the low expression levels have made it unexpectedly difficult to precisely identify the adenosine receptor subtypes present along the renal vasculature. Global expression in rat renal cortical and medullary tissue has been shown for all four adenosine receptors at both the mRNA and protein levels (29, 40, 93). Studies in a preglomerular vessel preparation containing arcuate and interlobular arteries as well as afferent arterioles have identified the presence of A_1AR protein and mRNA, but this approach does not resolve the expression profile along the longitudinal axis of the preglomerular vasculature (29). By in situ hybridization, cortical A_1AR mRNA was found exclusively at the glomerular vascular pole but not over the glomerulus itself (83). Although it is unclear whether the signal originated in granular, extraglomerular mesangial, or vascular smooth muscle cells, one may conclude that some cells at the glomerular vascular pole express A_1AR at much higher levels than any other vessel. RT-PCR assessment of A_1AR mRNA expression has confirmed its presence in dissected glomeruli (88). More recently, immunohistochemical evidence has suggested the presence of A_1AR expression in glomerular vessels, presumably in afferent arterioles, and inside the glomerulum, presumably in mesangial cells (71). However, of two antibodies directed against different epitopes, only one showed positive staining, an observation that cautions against overinterpretation of antibody-based evidence. In regard to A_2 receptors, it has been reported that preglomerular vessels express only the low-affinity A_{2b}AR at high levels but not the high-affinity A_{2a}AR receptor protein (29). In situ hybridization failed to detect either A_{2a}AR or A_{2b}AR mRNA in the renal cortex (83). The profile of adenosine receptor expression in efferent arterioles has not been determined with any degree of certainty. In outer medullary descending vasa recta, RT-PCR analysis revealed expression of A_1AR, A_{2a}AR, and A_{2b}AR, which was verified by Southern blotting (33). Receptor-binding studies using the well-defined panel of stable and selective ligands for adenosine receptor subtypes have not been performed in renal vascular tissue. In conclusion, the functional clues that can be derived from expression studies are relatively limited, but it seems clear that A_1AR are predominantly expressed in afferent arterioles. A_2AR, mostly A_{2b}AR, are present in all preglomerular vessels and in descending vasa recta. No reliable information is available for efferent arterioles.

ADENOSINE-INDUCED RENAL VASOCONSTRICTION

Effect of Adenosine at the Organ Level

There is abundant evidence to show that bolus injections of adenosine cause an immediate reduction in renal blood flow reflecting the response to activation of high-affinity A_1AR (24, 56, 77, 81). Because this blood flow response was seen when adenosine was injected in the renal artery, it is not mediated by systemic consequences of adenosine such as a reduction in blood pressure (24, 54). A reduction in renal blood flow was also observed during continuous administration of adenosine, but this decrease was only short lasting and waned within 1–2 min. The transient constrictor effect was blocked by nonspecific and A_1AR-specific antagonists, and it is absent in A_1AR knockout mice, indicating that it is mediated by activation of A_1AR (3, 54). This is supported by the persistent reduction in renal

blood flow and glomerular filtration rate (GFR) induced by the infusion of the A_1AR-specific agonist cyclohexyladenosine (CHA; see Ref. 13). In the isolated perfused kidney, CHA causes increasing vasoconstriction in the dose range between 10^{-9} and 10^{-7} M, whereas concentrations $>10^{-6}$ M cause vasodilatation no doubt because of spillover onto A_2AR with undefined vascular localization (43, 46). On the basis of hemodynamic modeling, the reduction in renal blood flow was attributed to a preglomerular, presumably afferent, arteriolar vasoconstriction (43, 77). The administration of A_1AR antagonists does not usually cause major increases in renal blood flow, suggesting either that A_1AR activation does not contribute to renal vascular resistance under resting conditions or that the effect of the inhibitors is incomplete (3, 34). GFR, on the other hand, is typically increased by A_1AR antagonists (5, 41, 86).

Effect of Adenosine in Glomerular Arterioles

Superficial afferent arterioles. Micropuncture studies in dogs have shown that an intrarenal adenosine infusion caused a doubling of preglomerular arteriolar resistance (58). In rats, adenosine caused a fall in glomerular capillary and welling point pressures and a fall in superficial nephron GFR (SNGFR), results consistent with preglomerular arteriolar vasoconstriction (22). In contrast to the transient reduction in renal blood flow, the effects of adenosine on SNGFR were persistent. Thus the constrictor response in superficial nephrons occurs in the absence of changes in renal plasma flow and with only small or no changes in kidney GFR (57, 58). These observations appear to be internally inconsistent, but it is possible that there is an unusual overrepresentation of A_1AR in afferent arterioles of the very superficial nephron population. Concordant with a tonic constrictor effect of adenosine in these nephrons are observations showing that inhibition of A_1AR with 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) or CVT-124 caused afferent arteriolar vasodilatation and an increase in both SNGFR and kidney GFR (5, 41, 86).

The effect of adenosine on arteriolar tone has been studied more directly in preparations that permit visualization of vessel diameters and that are not restricted to a selected population of vessels. Furthermore, in these in vitro preparations, the testable adenosine concentrations include the subnormal range, thereby facilitating the detection of A_1AR-mediated effects. In afferent arterioles of neonatal hamster kidneys transplanted in the cheek pouch of adult animals, adenosine, topically applied through micropipettes, caused dose-dependent vasoconstriction of afferent arterioles, whereas it dilated the arterioles of the cheek pouch itself (30). In isolated perfused afferent arterioles from the rabbit, addition of adenosine to the bath caused vasoconstriction in a dose-dependent fashion (84). Effects consisted of a 30% reduction in vessel diameter in proximal parts of the arteriole with maximum effects being reached at 10^{-6} M and smaller effects at higher concentrations, indicating that in this part of the arteriole A_1AR-mediated vasoconstriction is partially counteracted by A_{2b}AR-dependent vasodilatation as adenosine concentrations increase. It is consistent with this interpretation that the vasoconstriction caused by the A_1AR agonist CHA was slightly greater than that caused by adenosine and that it increased over the entire concentration range from 10^{-9} to 10^{-4} M (84). However, in the afferent arteriole in the immediate vicinity of the glomerulus, adenosine caused a monotonic vasoconstriction consisting of a 45% reduction in vessel diameter at 10^{-4} M, the highest concentration tested (Fig. 1). The absence of a discernible vasodilator effect at concentrations at which A_{2b}AR should be activated indicates that the short section of the afferent arteriole close to and inside the glomerulus is unique in that A_1AR-induced constriction does not appear to be opposed by A_2AR to a detectable extent. Recent experiments in isolated afferent arterioles from the mouse indicate a similar effectiveness of abluminal adenosine to vasoconstrict the vessel, particularly at

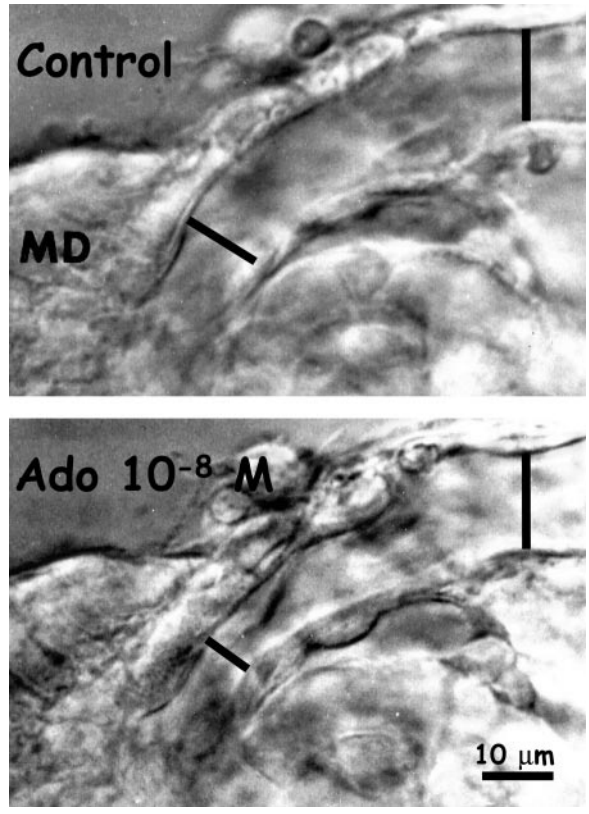

Fig. 1. Photomicrograph showing the effect of adenosine (Ado; 10^{-8} M) on the diameter of a perfused afferent arteriole from rabbit kidney. Note that there is a marked reduction in the luminal diameter of the arteriole at a narrow region at the entrance of the vessel into the glomerulus, just before the first branching of the arteriole, and that the region of highest sensitivity to adenosine is close to the macula densa (MD) cell plaque. This region showed vasoconstriction up to a concentration of 10^{-4} M adenosine. In contrast, the arteriole further upstream did not show measurable constriction at the 10^{-8} M concentration. Because of specimen positioning, this segment of high sensitivity is not visible in most preparations. Photograph taken by H. Weihprecht (84). Black bars define inner vascular diameters at indicated locations.

its glomerular entrance segment. The origin of the arterioles used in both the rabbit and mouse studies was the midcortical and outer cortical region, so that arterioles from true juxtamedullary nephrons were not included. Our results are apparently different from the net vasodilator effect of CHA in the isolated perfused kidney that was seen at perfusate concentrations of 10^{-5} M and higher (43, 46). Thus the A_2AR activated by high CHA concentrations and determining total renal vascular resistance in the whole kidney are localized on vascular segments other than afferent arterioles.

In the hydronephrotic kidney preparation, another technique permitting direct observation of arteriolar responses, the effect of adenosine appears to be transient. With topical application, adenosine caused a dose-dependent vasoconstriction over the 10^{-6} to 10^{-4} M dose range that faded within 1–2 min, and a similar effect was seen in an in vitro perfused hydronephrotic kidney with luminal application (20, 78). There was no noticeable steady-state effect of adenosine in the afferent arterioles, whereas interlobular arteries and efferent arterioles showed steady-state vasodilatation at a concentration of 10^{-5} M (20). The abluminal administration of CHA, in contrast, had effects comparable to those found in isolated vessels. These effects consisted of a stable diameter reduction that was dose dependent in the range between 10^{-8} and 10^{-6} M and that was most pronounced in the distal part of the arteriole where it caused a maximum effect of about −50%. The reduction in vascular diameter was accompanied by a reduction in glomerular blood flow by 30–40% at 10^{-7} M and by >50% at 10^{-5} M (15, 27). Although NECA vasodilated all preglomerular vascular segments up to the arcuate arteries, it caused no change or even a small constriction in the distal afferent arteriole (16, 27). Although NECA is not a specific A_2 agonist, this finding provides additional support for the notion that the distal afferent arteriole is unique in its predominant expression of A_1AR. In view of the normal actions of CHA, the waning effect of adenosine in this preparation may reflect an increased expression of dilatory A_2AR. It is also of note that at least in the in situ hydronephrotic kidney model the starting level for the adenosine addition studies are the prevailing tissue and plasma adenosine levels, not an adenosine-free condition.

Juxtamedullary afferent arterioles. Studies of the effect of adenosine in juxtamedullary arterioles are important in view of the notion that medullary blood flow may be regulated by adenosine in a way that is opposite to cortical blood flow regulation. Juxtamedullary afferent arterioles, studied in a blood-perfused preparation, respond to abluminal application of adenosine at 10^{-6} and 10^{-5} M with a marked transient and a smaller steady-state reduction of vessel diameter that was prevented by the A_1AR antagonist KW-3902 and magnified by A_{2a}AR inhibition (11, 28, 47). At concentrations $>10^{-5}$ M, the effect of adenosine was vasodilatation of juxtamedullary afferent arterioles that was partially inhibited by the A_{2a}AR antagonist KF-19837 (47). Diameter evaluations in these studies were made at a distance of 100 μm from the glomerulus and did not distinguish between proximal and distal regions of afferent arterioles. Although the steady-state effect of adenosine in these studies was relatively small, it may be relevant to point out that a 10% reduction in vessel diameter translates into a 50% increase in vessel resistance.

The response of afferent arterioles of juxtamedullary nephrons to CHA in the hydronephrotic kidney preparation consisted of a dose-dependent diameter reduction in the tested concentration range of 10^{-8} to 10^{-6} M that was about one-half that seen in more superficial arterioles (16). Concomitantly, glomerular blood flow was reduced by ~40% at 10^{-6} M, a response that was smaller than seen in superficial nephrons. In contrast to superficial arterioles, NECA had a small dilator effect in juxtamedullary afferent arterioles. These studies indicate that afferent arterioles of juxtamedullary nephrons may be less responsive to adenosine than arterioles from superficial or midcortical nephrons but that they respond qualitatively similar. Based on the functional information furnished by CHA and NECA, one would conclude that afferent arterioles of juxtamedullary nephrons have a lower expression level of functional A_1AR and a higher level of A_2AR compared with superficial arterioles (16). Nevertheless, the dilator action of A_1AR inhibition indicates that, in juxtamedullary afferent arterioles, the dominant effect of adenosine up to a concentration of 10 μM is vasoconstriction.

It is unclear to what extent a loss of A_1AR-mediated constrictor efficiency is responsible for the fleeting reduction in total renal blood flow caused by systemic adenosine, but the following aspects seem pertinent. The maintenance of constriction in afferent arterioles for extended periods of time noted in the observational studies indicates that A_1AR in afferent arterioles do not undergo rapid desensitization, the waning of a functional response during prolonged or repeated exposure of a receptor to its ligand (27, 30, 47). Most notably, in recent experiments in isolated afferent arterioles from the mouse, vasoconstriction caused by adenosine was observed to last for up to 30 min (Hansen PB, unpublished observations). The persistent nature of the A_1AR-induced vasoconstriction of afferent arterioles is consonant with the evidence from a number of studies indicating that the desensitization of native A_1AR in response to prolonged exposure to an agonist occurs in a time frame of hours to days (60). Furthermore, the inhibition of forskolin-stimulated adenylate cyclase activity in CHO cells expressing the human recombinant A_1AR was unaffected by a 30-min treatment with an A_1AR agonist (59). We consider it unlikely that the propensity of A_1AR to desensitize varies between different preparations and between A_1AR expressed in different segments of the renal vasculature.

Because the adenosine effects in vivo are assessed in a more complex environment than those encountered in vitro, it is possible that differences in the presence of

some modulating factor account for the apparent difference in the constrictor potential of adenosine seen in vivo and in vitro. The most intensely studied modulator of A_1AR-mediated constrictor actions is ANG II. There is abundant evidence to show that a reduction in ambient ANG II levels and the prevention of ANG II formation and action cause a marked attenuation of the vasoconstrictor response of the intact kidney to adenosine (15, 23, 56, 73, 85). Conversely, an elevation of ambient ANG II concentrations enhances the constrictor effect of A_1AR activation by adenosine or A_1AR-specific ligands (56, 85). Nevertheless, it is not clear that differences in ambient ANG II levels can explain the different responses of intact kidneys and isolated preparations. One would expect ambient ANG II concentrations to be lower in the artificial environment, and adenosine responses should therefore be blunted, the opposite of what is actually observed. The possibility that A_1AR-mediated vasoconstriction is dependent on the state of arteriolar innervation is not supported by studies showing an unaltered constrictor response to an A_1AR agonist in denervated compared with innervated kidneys (61). These results do not lend support to the possibility that the absence of nervous input in the isolated preparations importantly modifies their adenosine response.

Because the studies examining the effect of adenosine on renal blood flow in the whole kidney have been performed during systemic administration of adenosine, whereas the in vitro experiments were typically done during abluminal adenosine application, the possibility exists that the strength of the constrictor response varies with the route of administration. In support of a sidedness in the vascular actions of adenosine, we recently observed using laser-Doppler flowmetry in mice that adenosine given intravenously caused an increase in superficial renal blood flow, whereas the infusion of adenosine in the interstitial region below the flow probe caused a reduction in blood flow (Hashimoto S, unpublished observations). Furthermore, the vasoconstriction of isolated perfused afferent arterioles from the mouse caused by the bath addition of adenosine was not seen when adenosine was added to the luminal perfusate (Hansen PB, unpublished observations). In a study comparing the effects of intravenous infusion of high- and low-molecular-weight polyadenylic acids on renal blood flow in dogs, it has been noted that the low-molecular-weight compound (mol wt 5,000) caused transient vasoconstriction like adenosine, whereas the high-molecular-weight compound (mol wt 100,000) caused an exclusive and long-lasting vasodilator response that was inhibited by theophylline (79). The authors concluded that adenosine causes A_2AR-mediated vasodilatation through an intravascular site, whereas the A_1AR causing vasoconstriction are normally accessed from the interstitial aspect of the vessel. The causes for this sidedness of the effect of adenosine need to be explored further. It is conceivable, although unproven, that A_1AR are present in endothelial cells along the renal vasculature and that adenosine causes the release of nitric oxide (NO) and perhaps other endothelial vasodilators when administered from the vascular but not from the interstitial aspect of the vessel. The resulting A_1AR-induced constriction would therefore be blunted by endothelial factors only when adenosine is given intravascularly. In a study in dogs, the administration of nitric oxide synthesis (NOS) inhibitors caused a marked augmentation in the constrictor response of renal blood flow to bolus injections of adenosine while the dilator effect of the A_2 agonist CGS-21680 was unaffected, indicating that adenosine may cause NOS activation through an A_1AR-mediated mechanism (52). Enhancement of A_1AR agonist induced vasoconstriction by N^G-nitro-L-arginine methyl ester, and a marked left shift of the dose-response relationship between adenosine concentration and vasoconstrictor response has also been observed in the rat (7, 63). Studies showing a similar left shift in the adenosine dose-response curve during application of indomethacin suggest that a vasodilator prostaglandin may be another endothelial factor opposing A_1AR-mediated constriction (62). The results of these studies do not establish that A_1AR activation is directly coupled to the release of NO or prostaglandins since they are also compatible with the possibility that the constrictor effect of adenosine is merely enhanced by the removal of a constitutive vasodilator influence. It is also of note that adenosine administered in the vascular space must cross the endothelial cell layer to interact with smooth muscle cells. In addition to being a potential physical barrier to the movement of adenosine, endothelial cells from coronary blood vessels have been shown to rapidly metabolize adenosine with incorporation into various nucleotide pools (45). These authors suggest that, in coronary vessels, transvascular adenosine movement may be impeded more by this metabolic barrier function of the endothelium than by its physical properties. If the endothelium restricts the movement of adenosine, one would expect differences in receptor accessibility dependent on the route of administration.

In summary, adenosine administered from the vessel outside causes a marked, nontransient vasoconstriction in afferent arterioles from all regions of the kidney, although vessels of superficial nephrons appear to be more sensitive than arterioles of juxtamedullary nephrons. In the afferent arteriole at the glomerular entrance, the diameter reduction is monotonically dose dependent, indicating the absence of adenosine receptors opposing vasoconstriction. In the more proximal part of the arteriole, the vasoconstrictor effect of adenosine is blunted (at lower concentrations by A_{2a}AR and at higher concentrations by A_{2b}AR), but net vasodilatation does not occur. In the hydronephrotic kidney preparation, the adenosine-induced vasoconstriction is transient, an effect that may reflect changes in the vascular response pattern resulting from chronic elimination of the tubular epithelium. For reasons that are not entirely clear, A_1AR activation appears to cause a more pronounced constriction of

afferent arterioles when added to the interstitial aspect of the vessel.

ADENOSINE AND RENAL VASODILATATION

Effect of Adenosine at the Organ Level

In contrast to bolus injections, adenosine administered by constant infusion is associated with an unchanged or usually even increased renal blood flow (23, 54, 58, 77). The causes for the steady-state vasodilatation have been ascribed to preferential relaxation of the efferent arteriolar or medullary vascular beds, but a convincing argument for either explanation cannot be made on the basis of studies at the organ level. Nevertheless, the selective A_2AR agonist CGS-21680A elicits a monophasic reduction in renal vascular resistance, clearly indicating that activation of A_2AR is the cause for the transient nature of the renal constrictor response to adenosine (35). Furthermore, vasodilatation was seen in isolated perfused kidneys with the somewhat A_2AR-specific agonist NECA (43, 46). It is noteworthy that GFR is typically suppressed by adenosine in a more persistent fashion so that a reduction of filtration fraction is an invariable consequence of prolonged adenosine administration.

Even though obvious, it is relevant to point out that the infusion studies discussed above examine the effect of an addition of adenosine to the existing endogenous nucleoside levels and therefore limit the analysis to the supranormal concentration range. A consideration of the baseline adenosine concentrations in plasma and in the renal interstitial fluid may therefore be helpful to predict the expected changes in receptor engagement with adenosine infusions, taking into account the known affinity and dissociation constants of the different adenosine receptors. Plasma adenosine levels have been reported to be somewhere between 100 nM and 1 μM, i.e., in the 10^{-7} to 10^{-6} M range (12, 18, 32, 89, 91). Renal interstitial concentrations of adenosine as determined by microdialysis have been found to be between 50 and 200 nM in the cortex and between 160 and 210 nM in the medulla (6, 48–50, 70, 92). Thus these levels are in the same order of magnitude as plasma concentrations. The classical early analysis of ligand binding kinetics to the various adenosine receptors has established that A_1AR and A_{2a}AR have affinity constants for adenosine in the order of 10^{-8} M, whereas the affinity of A_{2b}AR is much lower, around 10^{-5} M (14, 19, 37, 82). Thus, at the prevailing extracellular adenosine concentrations of $\sim 10^{-7}$ M, one would expect A_1AR and the high-affinity A_{2a}AR to be partly occupied, whereas A_{2b}AR are probably not. The absence of a major effect of nonspecific AR inhibitors such as theophylline or aminophylline on renal hemodynamics is consistent with the notion that resting renal vascular tone represents a state of balanced A_1AR and A_{2a}AR activation (9, 54, 64). The increments in adenosine concentration resulting from the infusion should mostly be targeted to the A_{2b}AR receptor pool. For this simple reason, it is perhaps not surprising that adenosine infusions result in relaxation of all vessels expressing A_{2b}AR, the majority of the renal vasculature, and therefore cause global renal vasodilatation. In view of the evidence discussed above that the afferent arteriole near the glomerulus may not vasodilate even at elevated levels of adenosine, at least when adenosine is administered from the interstitial side, it is relevant to point out that the afferent arteriole is not the only resistance vessel in the kidney. Aside from the significant contribution of the efferent arterioles, interlobular arteries in the rat kidney have been estimated to represent as much as 50% of renal preglomerular resistance (8, 26) and have also been shown to contribute importantly to autoregulatory adjustments of renal vascular resistance (25). Furthermore, the renal artery has been shown to regulate renal vascular resistance by the release and downstream action of endothelium-derived vasodilators (31). Therefore, global renal vasodilatation may well occur in the absence of overt vasodilatation in afferent arterioles.

It is now well recognized that the majority of vasodilator agents act by binding to their receptors on endothelial cells and by eliciting the generation and release of endothelial relaxing factors, most notably NO, endothelial hyperpolarizing factor, and prostaglandins. The presence of A_2AR in endothelial cells of the renal vasculature has not been established directly, but a number of studies in various excised vessel preparations indicate that adenosine-induced vasodilatation is probably to some extent endothelium dependent. In the majority of these studies, adenosine appears to augment NOS activity and NO release through an A_2AR-mediated process, an action that would enhance the dilator component rather than diminish the constrictor component of the adenosine actions (1, 21, 38, 75, 90). In addition, adenosine has also been reported to dilate rabbit renal arteries through an endothelial relaxing factor that does not appear to be NO (66). Finally, adenosine has been shown to consistently stimulate the production of NO in cultured endothelial cells, usually through an A_2AR-dependent mechanism (36, 53, 87). Thus, in addition to the possible blunting of A_1AR-induced vasoconstriction as discussed above, endothelial dilator factors generated in response to A_2AR activation may enhance renal vasodilatation, thereby contributing to the waning renal constriction in the kidney during intravenous administration.

The overall conclusion from these studies at the organ level would be that the intravenous administration of exogenous adenosine, i.e., an elevation of plasma adenosine concentrations above normal, causes a short-lasting net vasoconstriction mediated by high-affinity A_1AR. However, this effect is overcome, at the elevated plasma adenosine levels resulting from the addition of exogenous nucleoside, by the simultaneous activation of lower-affinity A_2AR so that the dominating and lasting effect is net vasodilatation in most cases.

Effect of Adenosine in Efferent Arterioles

Dilatation of efferent arterioles has been suggested as one of the reasons for the return of renal blood flow to normal or supranormal values during an adenosine infusion, a notion that is mainly based on the observed reduction in filtration fraction (42, 77). However, it has been difficult to establish an unequivocal vasodilator action of adenosine in preparations in which the arteriole can be observed directly. In the blood-perfused juxtamedullary nephron preparation, the effect of adenosine on the diameter of efferent arterioles was qualitatively similar to that seen in afferent arterioles consisting of a stable diameter reduction by ~6% at a concentration of 10^{-5} M, a constrictor effect that was smaller than that seen in afferent arterioles (11, 47). Vasodilatation in the presence of an A_1AR blocker, and enhanced constriction in the presence of an A_{2a}AR blocker, resembled the effects noted in afferent arterioles. On the other hand, in the hydronephrotic kidney, adenosine at 10^{-5} M caused a steady-state diameter increase of ~14% that was not changed much by the A_1AR antagonist DPCPX but was abolished by the A_2AR antagonist 3,7-dimethyl-L-propargylxanthine (20). These results suggest the absence of A_1AR in efferent arterioles in this preparation, a notion supported by previous reports using the same preparation in which the A_1AR agonist CHA caused only small or no diameter reductions in efferent arterioles up to a concentration of 10^{-5} M (16, 27). In contrast, NECA induced a small efferent vasodilatation and an increase in glomerular blood flow (27). Thus adenosine effects in the efferent arteriole are not very pronounced and appear to consist of small constrictions at lower and small dilations at higher concentrations. The small magnitude of both constrictor and dilator effects suggests rather low levels of expression for all receptor subtypes. Overall, we conclude that a dilator effect of efferent arterioles may contribute to the loss of net vasoconstriction at elevated adenosine levels but that it is unlikely to account for the full dilator action of adenosine.

Adenosine and medullary blood flow. Vasodilatation of the vessels controlling renal medullary blood flow has been proposed as being responsible for the net vasodilatation of the kidney in response to continuous intravenous infusion of adenosine. Renal blood flow distribution measured with microspheres showed an increase in inner cortical blood flow, whereas outer cortical blood flow was unchanged (72). The magnitude of this increase varied between 23 and 94%, depending on the renin status of the dogs. Interstitial infusion of adenosine induced an increase in medullary blood flow measured with laser-Doppler flowmetry by ~40% (2). Direct infusion of adenosine in the renal medulla caused an ~25–30% increase in both outer and inner medullary blood flows (92). Direct assessment of blood flow in single inner medullary vasa recta by videomicroscopy showed an increase in red cell velocity without a diameter change only during intrarenal adenosine infusion at the highest dose tested (39). The infused amounts did not induce significant changes in inulin or *p*-aminohippuric acid clearances. In isolated perfused outer medullary vasa recta, the administration of increasing concentrations of adenosine induced a biphasic response, consisting of a vasoconstriction in the dose range between 10^{-11} and 10^{-7} M and a vasodilatation at 10^{-6} to 10^{-5} M (68). In contrast to cortical resistance vessels, administration of adenosine to vasa recta preconstricted by ANG II leads to vasodilatation (68, 69). The concentration of adenosine in the interstitial fluid of the medulla is between 10^{-7} and 10^{-6} M, a level where one may expect not much impact on resting tone but where an increase of adenosine concentration should cause vasodilatation (70, 92). In summary, most studies agree that the administration of adenosine causes an increase in medullary blood flow by relaxing both juxtamedullary afferent and perhaps efferent arterioles and outer medullary vasa recta pericytes. Nevertheless, for quantitative reasons, we consider it unlikely that this increase in medullary blood flow can be the only reason responsible for the overall increase in total renal blood flow seen with constant infusions of adenosine. Medullary blood flow represents only ~10% of total renal blood flow. Thus a reduction in cortical blood flow by 50% would require a more than fivefold increase in medullary flow for compensation. The magnitude of the observed increase in medullary blood flow, variable as it may be, is not even close to this expectation. Thus much of the compensatory increase in total renal blood flow in response to continuous adenosine infusions must take place in the renal cortex.

In conclusion, the intravenous infusion of adenosine, i.e., an increase of plasma adenosine levels above normal, causes a renal vasodilator response that is the result of A_2AR-mediated vasorelaxation in most parts of the renal vasculature, including larger renal arteries, juxtamedullary afferent arterioles, efferent arterioles, and medullary vessels (Fig. 2). A combination of

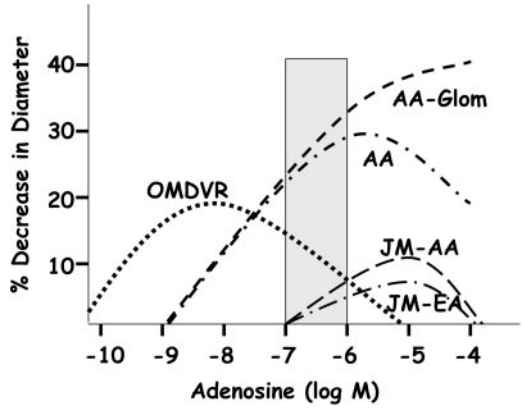

Fig. 2. Relationship between the concentration of adenosine and the %decrease in the diameter of afferent arterioles near the glomerulus (AA-Glom), proximal afferent arterioles (AA), juxtamedullary afferent arterioles (JM-AA), juxtamedullary efferent arterioles (JM-EA), and outer medullary descending vasa recta (OMDVR). There are no data for the missing vessels. Diameter decrements are a measure of vessel resistance. Data are from Refs. 47, 68, and 84.

these effects, rather than one single action, is responsible for the relaxation caused by exogenous adenosine in the whole kidney. A_2AR-mediated vasorelaxation may be facilitated by intravascular receptors, most likely on endothelial cells, causing the release of NO and other endothelial relaxing factors. In contrast, the afferent arteriole, especially in the segment closest to the glomerulus, responds to adenosine with vasoconstriction over a wide concentration range. Afferent arteriolar A_1AR are selectively activated from the interstitial aspect of the vessel, a characteristic that is ideally suited for the presumed physiological role of these receptors, the mediation of the TGF response.

DISCLOSURES

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